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Original

Relationship of circulating levels of 25(OH) vitamin D with parathyroid hormone in Iranian patients with chronic kidney disease not yet on dialysis; what is the best threshold for 25(OH) vitamin D

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Abstract

Introduction: Mineral and bone disorders are common in patients with chronic kidney disease (CKD). Vitamin D plays an important role in calcium-phosphorus balance.

Objectives: The main aim of this investigation is to assess the relation between circulating levels of 25(OH) vitamin D and parathyroid hormone (PTH) and estimating the best threshold of vitamin D which may prevent secondary hyperparathyroidism.

Patients and Methods: This cross-sectional study was conducted between January 2014 to September 2015. Adult patients with CKD who were not on routine peritoneal dialysis or hemodialysis and did not receive any kidney transplantation, enrolled to this study. Patients who were pregnant or who were on vitamin D supplementation therapy were excluded. Basic demographic and laboratory information were measured.

Results: Around 254 patient enrolled in this study (55.1% men). The prevalence of vitamin D deficiency and insufficiency were significantly high, 12.6% and 53.9%, respectively. Serum PTH level increased significantly as circulating plasma level of 25(OH) vitamin D decreased ($P=0.003$). Serum total calcium increased significantly with high levels of plasma 25(OH) vitamin D ($P<0.001$) and hypercalcemia was seen in 2.8% of patients. Piecewise linear regression modeling of PTH for 25(OH) vitamin D estimated the best threshold for 25(OH) vitamin D of 13.00 ng/mL (95% CI: 2.55-23.44 ng/mL) ($P=0.015$).

Conclusion: This study again confirms this fact that sufficient level of serum 25(OH) vitamin D is mandatory in patients with CKD in order to prevent secondary hyperparathyroidism. Although this study recommends level of serum 25(OH) vitamin D to be above 13 ng/mL for this purpose.

Keywords: Renal insufficiency, Chronic, Hyperparathyroidism, Vitamin D, Parathyroid hormone, Renal osteodystrophy

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Introduction

Chronic kidney disease (CKD) is an increasing health problem all around the world and is among one of the most important non-communicable diseases which can elevate cardiovascular mortality up to 10 times (1). Mineral and bone disorders are common in patients with CKD and are an important cause of decreased quality of life and increased in morbidity and cardiovascular mortality (2). The pathophysiology of mineral and bone disorders is very complex and is related to interaction between intestine, kidney and bone. Body, faces to a vicious cycle in response to declining renal function. Impairment in phosphate excretion results in elevated level of serum phosphorus and decreasing in synthesis of bioactive form of vitamin D. Since the main goal of this complex system is to maintain the balance between calcium and phosphorus, the mentioned changes give rise to increased synthesis and secretion of parathyroid hormone (PTH) and parathyroid hyperplasia which finally bring about secondary hyperparathyroidism (3,4).

Vitamin D and its bioactive form, 1, 25(OH) 2 vitamin D or calcitriol plays an important role in calcium-phosphorus balance. Calcitriol which is in interaction with its receptor in parathyroid glands, suppress secretion of PTH (5). Thus vitamin D deficiency which is actually very common among patients with CKD (6,7), causes increasing in serum level of PTH and accounts one of the most important basics in the formation of secondary hyperparathyroidism in patient with CKD (8,9). Also it is worth mentioning that some studies have demonstrated

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Implication for health policy/practice/research/medical education

In a cross-sectional study on 254 chronic kidney disease (CKD) patients not yet on dialysis, we found, sufficient level of serum 25(OH) vitamin D is mandatory in patients with CKD in order to prevent secondary hyperparathyroidism. Although this study recommends level of serum 25(OH) vitamin D to be above 13 ng/mL for this purpose.

non-skeletal benefits of vitamin D. They have revealed that vitamin D deficiency is associated with albuminuria and higher prevalence of cardiovascular mortality (10,11). Some others showed association between vitamin D deficiency and risk factors for cardiovascular disease such as hypertension (12). Likewise, some studies found a relationship between vitamin D deficiency and mortality in patients with CKD too (13).

Moreover, numerous studies have shown that treatment with different forms of vitamin D (both vitamin D2, ergocalciferol and vitamin D3, cholecalciferol) decreases the level of plasma PTH and prevalence of secondary hyperparathyroidism (14-16). However, they did not recommend routinely prescribed vitamin D to suppress PTH in the absence of vitamin D deficiency (17). Although many studies agreed on a threshold level of 10 ng/mL (25 nmol/L) as a cut-point for vitamin D deficiency, however, this level is accompanied with muscle weakness, bone pain, fractures and increased level of PTH (18). Indeed, there is no agreement on the best threshold for plasma level of vitamin D to prevent secondary hyperparathyroidism in patients with CKD. "KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease", defines the level of vitamin D less than 20 ng/mL (50 nmol/L) as vitamin D deficiency, but did not instruct any level for vitamin D insufficiency, especially when discussing the proper level to prevent secondary hyperparathyroidism (17).

Objectives

The main aim of this investigation is to assess the relation between circulating levels of 25(OH) vitamin D and PTH and estimating the best threshold of vitamin D which may prevent secondary hyperparathyroidism.

Patients and Methods

Study population and study design

This cross-sectional study was performed in nephrology subspecialty clinic, Imam Khomeini Hospital Complex from January 2014 to September 2015. All adult patients with CKD stage 2 to 5 who were not on routine peritoneal dialysis or hemodialysis and did not receive any kidney transplantation in their life, enrolled to this study. Patients who were pregnant or who were on vitamin D supplementation therapy were excluded.

Measurements

We extracted basic demographic information from previous records and direct interview with patients. All patients were examined and their weight, height, systolic and diastolic blood pressure were measured. Etiology of CKD obtained from previous documents. All patients undergone routine laboratory studies with specific considerations on 25(OH) vitamin D, PTH, alkaline phosphatase, calcium and phosphorus.

We applied Modification of Diet in Renal Disease (MDRD) equation to calculate glomerular filtration rate (GFR) (19). Level of 25(OH) vitamin D concentration was measured in plasma by a radio-immunologic method (using Pars Azmoon kits). Normal values range from 10 to 30 ng/mL. Also we measured serum PTH concentration using second generation radio-immunometric assay. Phosphate concentration and total calcium were measured by colorimetry and specific electrodes, respectively.

According to plasma level of vitamin D, patients were categorized into three distinct groups; deficient (plasma level of 25(OH) vitamin D less than 10 ng/mL), insufficient (plasma level of 25(OH) vitamin D more than 10 ng/mL and less than 30 ng/mL) and sufficient (plasma level of 25(OH) vitamin D equal to or more than 30 ng/mL and less than 100 ng/mL).

Ethical issues

1) The research followed the tenets of the Declaration of Helsinki; 2) This study was reviewed and approved by Tehran University of Medical Sciences (TUMS) review board. All patients provided an informed consent signed by themselves or their legally authorized representatives.

Statistical analysis

STATA/MP version 12.0 for Windows was used to analyze data. Clinical and laboratory data described using numbers and percentages for qualitative variables, mean and standard deviation for normally distributed quantitative variables and median with interquartile range for skewed quantitative variables.

Shapiro-Wilk test used to assess normal distribution. Multi-group analysis were done using ANOVA/Kruskal-Wallis with post hoc tests. Relation between quantitative variables were analyzed using Pearson's correlation coefficient and Spearman's correlation coefficient. A cut-off point of 0.05 for statistical significance was presumed.

The relation between 25(OH) vitamin D and PTH concentration was modeled using piecewise linear regression. The 95% confidence interval (CI) of the estimated threshold for 25(OH) vitamin D was estimated with the bootstrap method and 1000 resamples. Local polynomial regressions of PTH for 25(OH) vitamin D was also performed using nonparametric regression model with LOWESS (locally weighted scatterplot smoothing).

Results

Patients' general characteristics

Table 1 shows the main characteristics of patients in this study. A total of 254 patients (mainly men) fulfilled the inclusion/exclusion criteria. About 20% of them were

Table 1. Characteristics of participated patients

	Mean (SD), Median (IQR), Number (%)
Age, y	61.91 (15.25)
Men, %	140 (55.1)
BMI, kg/m^2	27.58 (5.85)
Systolic blood pressure, mm Hg	132.00 (15.23))
Diastolic blood pressure, mm Hg	79.94 (5.98)
Total cholesterol, mg/dL	181.16 (47.46)
Hypertension, %	104 (40.94)
Diabetes mellitus, %	53 (20.86)
Glomerulonephritis, %	31 (12.20)
Renal stone, %	9 (3.54)
Polycystic kidney disease, %	6 (2.36)
Unknown, %	51 (20.07)
Serum albumin, g/dL	4.13 (0.46)
Urea*, mg/dL	74.00 (36.75)
Creatinine*, mg/dL	1.90 (1.00)
25(OH)D*, ng/mL	23.20 (19.22)
Intact PTH*, pg/mL	62.50 (63.00)
Total calcium, mg/dL	9.25 (0.72)
Phosphorus, mg/dL	3.98 (0.80)
Alkaline phosphatase*, IU/L	190.50 (109.5)
GFR, mL/min/1.73 m^2	36.99 (14.74)
CKD stages, %	
Stage 2 (60-89)	15 (5.91)
Stage 3a (45-59)	61 (24.02)
Stage 3b (30-44)	85 (33.46)
Stage 4 (15-29)	82 (32.28)
Stage 5 (<15)	11 (4.33)

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; PTH: parathyroid hormone; GFR, glomerular filtration rate; CKD, chronic kidney disease.
* Median and IQR for urea, creatinine, 25(OH), intact PTH and alkaline phosphatase.

obese (body mass index > 30 kg/m^2). Hypertension and diabetes mellitus were the most common underlying causes of CKD. CKD stage 3 encompass most of the CKD patients followed by stage 4. The prevalence of vitamin D deficiency and insufficiency were significantly high, 12.6% and 53.9%, respectively; only 33.5% of patients had sufficient serum level of vitamin D (Table 2).

Relation between different minerals and bone components

Serum PTH level increased significantly as circulating plasma level of 25(OH) vitamin D decreased ($P=0.003$) (Table 2). Although serum total calcium (adjusted regarding with serum level of albumin) increased significantly with high levels of plasma 25(OH) vitamin D ($P<0.001$) (Table 2). Hypercalcemia (adjusted serum total calcium > 10.5 mg/mL) was seen in 2.8% of patients, 1 in deficient, 2 in insufficient and 4 in sufficient vitamin D group. There were no significant differences in serum level of phosphorus or serum level of alkaline phosphatase in different groups of vitamin D (Table 2).

Table 3 shows correlations between serum intact PTH levels with 4 different components; i.e. serum total calcium, serum phosphorus, alkaline phosphatase and 25(OH) vitamin D. We found fair positive correlation between alkaline phosphatase and PTH ($P<0.001$), weak negative correlation between serum total calcium and PTH ($P=0.002$) and fair negative correlation between plasma level of 25(OH) vitamin D and PTH ($P<0.001$). We found no linear correlation between serum phosphorus and serum PTH level.

Relation between circulating level of 25(OH) vitamin D and PTH

As noted earlier, plasma level of PTH decreased as circulating level of 25(OH) vitamin D increased (Table 3). Piecewise linear regression modeling of PTH for 25(OH) vitamin D estimated the best threshold for 25(OH) vitamin D of 13.00 ng/mL (95% CI: 2.55-23.44 ng/mL) ($P=0.015$) (Figure 1). We ran piecewise linear regression modeling for log(PTH) and ln(PTH) versus log(vitamin D) and ln(vitamin D), but the most suited model was the one had used PTH for 25(OH) vitamin D as described earlier. It is notable that the estimated slopes were negative below and above the threshold, but not statistically significant (Table 4).

The smoothed curve between PTH and 25(OH) vitamin D using nonparametric regression model, LOWESS (locally weighted scatterplot smoothing) also showed a nonlinear relation with an inflection point around 13 ng/mL of 25(OH) vitamin D (Figure 2).

Discussion

The most important finding of this study is that the negative correlation between PTH and 25(OH) vitamin D in patients with CKD is nonlinear. The PTH hormone increases slowly as 25(OH) vitamin D decreases, but this hormone increases more rapidly with level of 13 ng/mL of 25(OH) vitamin D or lower values. This study also showed

Table 2. Calcium, phosphorus, alkaline phosphatase and PTH according to different circulating level of 25(OH) vitamin D

	Overall	25(OH) Vitamin D, ng/mL			*P* value
		<10	10–30	>30	
Number of subjects	254	32	137	85	-
Intact PTH, pg/mL	62.50 (63.00)	103.50 (117.85)	61.80 (56.70)	53.20 (55.35)	0.003
Toatl serum calcium*, mg/dL	9.33 (0.69)	9.03 (0.69)	9.27 (0.69)	9.56 (0.64)	<0.001
Serum phosphorus, mg/dL	3.89 (0.80)	4.13 (0.72)	3.98 (0.81)	3.92 (0.80)	0.433
Alkaline phosphatase, IU/L	190.50 (109.5)	206.00 (158.00)	187.00 (194.00)	195.00 (105.00)	0.139

Abbreviation: PTH: parathyroid hormone.
* Total serum calcium was corrected regarding to plasma albumin level.

Table 3. Calcium, phosphorus, alkaline phosphatase according to different circulating level of Intact PTH

	Intact PTH, pg/mL	
	Spearman's correlation coefficient	*P* value
Serum total calcium*, mg/dL	- 0.193	0.002
Serum phosphorus, mg/dL	0.039	0.54
Alkaline phosphatase, IU/L	0.242	<0.001
25(OH) vitamin D, ng/mL	-0.227	<0.001

Abbreviation: PTH: parathyroid hormone.
*Total serum calcium was corrected regarding to plasma albumin level.

Table 4. Correlation between PTH and 25(OH) vitamin D in the values, before and after the calculated threshold

	Coefficient	Standard error	P value
25(OH) D < 13 ng/mL			
Intercept	173.33	59.34	0.006
Slope	-5.57	6.90	0.424
25(OH) D > 13 ng/mL			
Intercept	104.54	14.33	<0.001
Slope	-0.61	0.39	0.123

Abbreviation: PTH: parathyroid hormone.

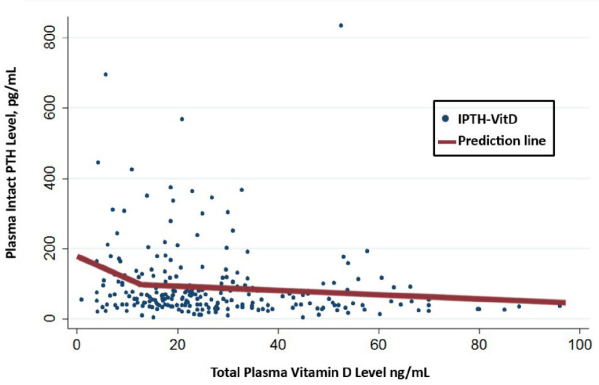

Figure 1. Piecewise linear regression model, Intact PTH according to 25(OH) vitamin D level. Best threshold at 13 ng/mL (95% CI: 2.55-23.44) of 25(OH) vitamin D ($P = 0.015$; $R^2 = 0.0378$).

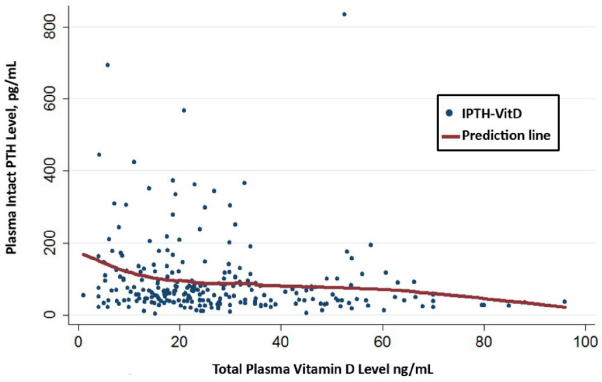

Figure 2. Non-parametric regression (LOWESS [locally weighted scatterplot smoothing]).

that if the 25(OH) vitamin D maintain in sufficient ranges (30 to 100 ng/mL), prevalence of hypercalcemia and extremely suppressed plasma PTH is extremely low.

One the main strength of this study is the assessment of calcium, phosphorus and alkaline phosphatase beside PTH and 25(OH) vitamin D. This, helped us to understand any abnormality in calcium-phosphorus balance along with changes in PTH and 25(OH) vitamin D. On other hand, this study showed that although sufficient level of 25(OH) vitamin D can prevent secondary hyperparathyroidism, but this does not cause any major abnormality in calcium, phosphorus and alkaline phosphatase level.

Different studies have shown that serum PTH level increases when 25(OH) vitamin D decreases in CKD patients (20,21) or even in healthy subjects (22,23). Up to our best knowledge, there are plenty of studies which found negative correlation between serum PTH and 25(OH) vitamin D level, especially in the range of 10 to 50 ng/mL (25-125 nmol/L) (24), but only few studies suggested a certain threshold for 25(OH) vitamin D to prevent secondary hyperparathyroidism (25,26), especially in adult patients with CKD (27). Some other studies also found this relation more complex and related to age and ethnicity of CKD patients (28,29). But with piecewise linear regression model and LOWESS, this study showed that circulating level of 25(OH) vitamin D more than 13 ng/mL retains serum level of PTH in a normal range and prevents secondary hyperparathyroidism in CKD patients. This study strongly recommend clinicians to improve serum level of 25(OH) vitamin D in CKD patients above 13 ng/mL to prevent secondary hyperparathyroidism. This means that level 30 ng/mL of 25(OH) vitamin D that was recommended by "National Kidney Foundation Kidney Disease Outcomes Quality Initiative and Kidney Disease: Improving Global Outcomes", may be sufficient for CKD patients. Although in comparison with different studies which suggested a threshold for 25(OH) vitamin to prevent hyperparathyroidism, this study suggests a lower threshold (21,26). It is worth mentioning that different studies have assessed the level of 25(OH) vitamin D as an associated marker for mortality and progression to end stage renal disease (ESRD) in CKD patients (30,31), but this study would not assess these effects of vitamin D.

This study has some limitations too. We measured 25(OH) vitamin D and linked it to bioactive form of vitamin D, also we know that 1,25(OH)2 vitamin D is the main active form of vitamin D. Due to lack of a very large sample size, we could not analyze the results of this study in different age, sex, renal function and ethnicity groups, but we know that PTH-vitamin D relation is a complex interplay with all these variables. Maybe we found different threshold in different subgroups while we take them into consideration.

In summary, this study again confirms this fact that sufficient level of serum 25(OH) vitamin D is mandatory in patients with CKD in order to prevent secondary hyperparathyroidism. Although this study recommends

level of serum 25(OH) vitamin D to be above 13 ng/mL for this purpose.

Limitations of the study

This is a single center study with a limited proportion of patients. We suggest larger studies on this subject.

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Authors' contribution

All authors, take part equally in the design and conducting the investigation and preparing the manuscript.

Conflicts of interest

There were no points of conflicts.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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